DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL

MINUTES OF MEETING

Immunization Practices Advisory Committee
June 3-4, 1991
Atlanta, Georgia

The Immunization Practices Advisory Committee (ACIP) met in Auditorium A at the Centers for Disease Control, Atlanta, Georgia, on June 3-4, 1991. Those in attendance are listed below:

COMMITTEE MEMBERS PRESENT

Dr. Samuel L. Katz, Chairman
Dr. James D. Cherry
Dr. Mary L. Clements
Dr. David W. Fraser
Dr. Caroline B. Hall
Dr. Carlos E. Hernandez
Dr. Gregory R. Istre
Dr. Mary E. Wilson

Ex Officio Members

Dr. Carolyn Hardegree (FDA)
Dr. John R. La Montagne (NIH)

Liaison Representatives

Dr. David Fedson (ACP)
Dr. Edward A. Mortimer, Jr. (AMA)
Dr. Georges Peter (AAP)
Dr. Michael Peterson (DoD)
Dr. William Schaffner, II (AHA)
Dr. Susan E. Tamblyn (NACI)
Dr. Ronald C. Van Buren (AAFP)

Executive Secretary

Dr. Claire V. Broome

NAVY ENVIRONMENTAL HEALTH CENTER

Capt. S. William Berg

HHS STAFF PRESENT

CENTERS FOR DISEASE CONTROL

Office of the General Counsel

Mr. Kevin M. Malone

Office of Health and Safety

Dr. Naima Abd Elghany
Ms. Jane Suen

CENTERS FOR DISEASE CONTROL (Cont'd)

Epidemiology Program Office

Dr. Melinda Wharton

Center for Infectious Diseases

Dr. Nancy Cox
Ms. Julia Garner
Dr. James Hughes
Dr. Harold Margolis
Dr. Brad Perkins
Dr. David Swerdlow

Center for Prevention Services

Dr. Bill Atkinson
Dr. Robert Chen
Dr. Stephen Cochi
Dr. Susan Davis
Ms. Rosamond Dewart
Dr. Vance Dietz
Dr. Laura Fehrs
Ms. Judy Gantt
Dr. Jacqueline Gindler
Dr. Mark Grabowsky
Dr. Stephen Hadler
Dr. Alan Hinman
Dr. Mary Lou Lindegren
Dr. Lauri Markowitz
Dr. Walter Orenstein
Dr. Peter Patriarca
Dr. Desiree Rodgers
Mr. Stephen Sepe
Dr. Raymond Strikas
Dr. Peter Strebel
Dr. Steve Wassilak
Dr. David J. West
Dr. Walter Williams

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

Dr. Frank Mitchell

FOOD AND DRUG ADMINISTRATION

Dr. Elaine Esber
Dr. Roland Levandowski

NATIONAL INSTITUTES OF HEALTH

Dr. Regina Rabinovich

OTHERS PRESENT

Ms. Jill Chamberlin, Vaccine Bulletin
Dr. Pinya Cohen, Connaught Labs
Dr. Bruce Dull, Preventive Medicine Associates
Jack Fleeman, Fleeman Pharmacy
Thomas R. Flippen, Lederle-Praxis Biologicals
Stephen Hildreth, Lederle-Praxis Biologicals
David M. Konys, Biogen, Inc.
Dr. Saul Krugman, New York University Medical Center
Carlton Meschievitz, Connaught Labs
George Moonsammy, Smith Kline Beecham
Ken Oliva, John Snow, Inc.
Brenda Patoine, Creamer Dickson Basford
Miguel Perea, Merck & Co.
Dr. Stanley A. Plotkin, Pasteur-Merieux-Connaught
Hal Rathfon, Smith Kline Beecham
Robert Scott, Lederle
Dr. Judith Shindman, Connaught Laboratories, Ltd.
Mr. Ted Vigodsky, WGST/WPCH
Dr. Jo White, Merck Sharpe & Dohme Research Labs
Dr. M. J. Winship, Lederle-Praxis Biologicals
Mr. Chris Zurawsky, Infectious Disease News, SLACK, Inc.

IMMUNIZATION PRACTICES ADVISORY COMMITTEE
Meeting at
Auditorium A
Centers for Disease Control
Atlanta, Georgia

AGENDA

June 3, 1991

| | | |
|---|---|---|
| 8:30 a.m. | Welcome and Opening Remarks | Dr. Samuel Katz<br>Dr. Claire Broome |
| 8:45 a.m. | DTP Statement | Dr. Steve Cochi |
| 10:00 a.m. | BREAK | |
| 10:30 a.m. | Hepatitis Statement | Dr. Harold Margolis |
| 12:00 noon | LUNCH | |
| 1:00 p.m. | Smallpox/Vaccinia Statement | Dr. William Atkinson |
| 1:30 p.m. | Update on Cholera Vaccines | Dr. David Swerdlow |
| 2:00 p.m. | Update on Group B Meningococcal Vaccines | Dr. Brad Perkins |
| 2:30 p.m. | BREAK | |
| 3:00 p.m. | Update on Measles Epidemiology<br>Measles Outbreak in New York City<br>Measles Vaccination of Children with URIs | Dr. William Atkinson<br>Dr. Susan Davis<br>Dr. Lauri Markowitz |
| 4:00 p.m. | Neonatal Tetanus Studies in Bangladesh | Dr. Gary Hlady |
| 4:30 p.m. | ADJOURN | |

June 4, 1991

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|---|---|---|
| 9:00 a.m. | Update on National Vaccine Program | Mr. Stephen Sepe |
| 9:30 a.m. | Update on Influenza Vaccines | Dr. Robert Chen |
| 10:00 a.m. | BREAK | |
| 10:30 a.m. | Immunization in Immunocompromised Individuals | Dr. Mark Grabowsky<br>Dr. Robert Chen |
| 11:30 a.m. | ADJOURN | |

5/31/91

## Executive Summary

On June 3-4, 1991, the ACIP met at the Centers for Disease Control (CDC) to discuss the status of numerous vaccine-preventable diseases and vaccine-related issues in the United States. Dr. Samuel Katz presided as Chairperson; Dr. Claire Broome was Executive Secretary of the ACIP Committee. The Committee decided on **meeting dates for 1992. They are: February 12-13; June 9-10; and October 21-22.**

Before moving to the items on the agenda, Dr. Broome reported that the executive secretaries of several of the CDC advisory committees met with the CDC Committee Management Officer, CDC Office of General Counsel, and the CDC ethics office about what the appropriate stance of CDC is regarding **alleged conflict of interest** of certain Committee members. She said the general consensus was that it would be inappropriate to exclude members with ties to the pharmaceutical industry, state health departments who receive federal funding and the like. Rather, it was felt that the appropriate position was to be sure that people were aware of relationships that could cause potential conflict of interest. The process of such disclosure is still being developed.

**Diphtheria-Tetanus-Pertussis (DTP)** issues, presented by Stephen L. Cochi, M.D., Division of Immunization (IM), Center for Prevention Services (CPS), were the first items on the agenda. After discussion of the changes incorporated as a result of the February ACIP meeting and suggestions for additional changes, the ACIP DTP Statement was accepted; publication in the *MMWR* will be arranged shortly.

**The Hepatitis ACIP Statement** was discussed next, following a presentation and summary by Harold Margolis, M.D., Division of Viral and Rickettsial Diseases (DVRD), Center for Infectious Diseases (CID). During this discussion, the ACIP voted unanimously to recommend universal immunization for infants, children, and adolescents, with the caveats that the emphasis is primarily on achieving universal coverage of infants and that immunization of teenagers is a relatively short-term event until the impact of universal immunization of infants is felt.

**The ACIP Vaccinia Statement** changes were presented by William Atkinson, M.D., M.P.H., IM, CPS. After some discussion, the ACIP voted that the statement not be published as written. A recommendation to issue recommendations about vaccinia vaccination for laboratory personnel was passed unanimously. Also passed was a decision to issue an informational statement--not a formal recommendation--suggesting that vaccinia vaccine be considered for certain groups of health-care workers.

David Swerdlow, M.D., Division of Bacterial and Mycotic Diseases

(DBMD), CID, gave an **overview of cholera in South America and the current recommendations regarding cholera vaccine**. The seventh pandemic of cholera is spreading rapidly in South America; the currently available vaccine is only thought to be 50% effective and is not recommended for general use; several investigational vaccines look promising, but large field trials in South America are needed; the risk to American travelers is low, and no changes in the ACIP recommendations are suggested.

Dr. Walter Dowdle, Deputy Director of the CDC, thanked all the members of the Committee for the work they do. He then announced that **Dr. James Cherry and Dr. Caroline Hall are rotating off the Committee after serving 4 years**, and presented them with certificates and medallions. Dr. Katz also announced that Dr. Stanley Broadnax, not present at this meeting, is also rotating off the ACIP.

Dr. Bradley Perkins, DBMD, CID, updated the group on **group B meningococcal vaccines**, particularly a Cuban one used extensively in Cuba and Brazil. He said that preliminary estimates of the vaccine efficacy of the Cuban vaccine in Brazil are lower than that found in Cuba. The results in Brazil suggest that this vaccine is not ready for widespread use.

Four **measles presentations** were made. Dr. William Atkinson reported that thus far in 1991, 5,400 cases of measles have been reported from 36 states. Only 21% of patients were appropriately vaccinated. There have been 21 deaths, for a case-fatality rate of about 3/1,000.

Dr. Susan Davis, IM, CPS, reported details of a large measles outbreak in New York City this year. As of May 31, 1991, 3,083 cases with 9 deaths have been reported. Preliminary data from a CDC investigation show that underreporting is greater than 40% and that the magnitude of the outbreak is greater than suggested by the number of cases reported.

Dr. Lauri Markowitz, IM, CPS, gave two presentations. First, she summarized a recent *JAMA* report, and two earlier studies in other countries, on the effect that upper respiratory infections have on children's seroresponse to measles vaccination. She concluded that CDC believes there should be no change to the ACIP recommendations that state that minor febrile illnesses are not a contraindication to measles vaccination; Committee members agreed. Then she gave a "for background" presentation on measles and vitamin A to see whether the ACIP would want to consider, at a future time, making recommendations about the use of vitamin A in the current measles epidemic in the United States. The Committee was not ready to prepare or issue a statement on this subject at this time.

Dr. Gary Hlady, Country Director, Bangladesh, Global 2000, Inc.,

reported on **studies documenting inefficacious tetanus toxoid produced and used in Bangladesh**; an estimated 9,000 cases of neonatal tetanus may have occurred in children born to women who had received two doses of this vaccine. This vaccine is currently produced in about 50 laboratories in 34 countries, raising questions about appropriate quality control mechanisms.

Mr. Stephen Sepe, IM, CPS, gave three related presentations. In the first, he discussed **the activities of the National Vaccine Program (NVP) since the release of the Measles White Paper** in February. An Immunization Education and Action Committee--a subcommittee of the Healthy Mothers, Healthy Babies Coalition--has been formed by the many voluntary organizations that have expressed an interest in doing something about the current measles epidemic. Chairperson of the subcommittee is Surgeon General Antonia Novello. This group met in April and has another scheduled meeting in mid-June. An Interagency Committee on Immunization has also been formed in response to the White Paper suggestion to coordinate immunization services of federal agencies. Its first meeting was on February 22; Dr. Ken Bart is chairperson.

Also two subcommittees have been created within the NVP. The Subcommittee on Access to Services will review third-party payment plans, focusing on barriers to access. Its first meeting was May 13; Dr. Ed Marcuse is chairperson. The Subcommittee on Vaccine Licensure and Regulation was formed to review specific licensing and regulatory processes and to recommend improvements in the licensing/regulatory process. Dr. Robert Gerety is chairperson. Its first meeting was held on May 9.

Mr. Sepe then updated the ACIP on the status of the **National Vaccine Injury Compensation Program**, which is overwhelmed by petitions and in a financial crisis; it will probably be out of money in June. A position paper on the subject is being drafted, and the Advisory Commission on Childhood Vaccines voted at its last meeting to have a moratorium on payments to petitioners.

Finally, Mr. Sepe summarized the **collaborative activities with the Office of the Surgeon General** regarding immunization. In addition to the activities already mentioned, she has named immunization as one of her top priorities; held immunization briefings; been involved in the Healthy Children Ready to Learn Initiative; helped create the Interagency Committee on Immunization; conducted site visits to problem areas; and is considering drafting a Surgeon General's Report on Immunization.

Robert Chen, M.D., IM, CPS, brought the Committee up-to-date on the **investigation of Guillain-Barre syndrome cases possibly associated with the 1990-91 influenza vaccination**. This investigation is continuing. Capt. S. William Berg of the Navy Environmental Health Center said that of 118,000 recruits

vaccinated as of the end of May, only 1 case of GBS had occurred, and that was in a recruit who had also received three other vaccinations. Dr. Chen reported that the Army reports no GBS cases among the 300,000 vaccinations given during Operations Desert Shield and Desert Storm.

Mark Grabowsky, M.D., M.P.H., IM, CPS, then reviewed a draft ACIP Statement on Immunization of Persons with Altered Immunocompetence, dated June 3, 1991. He outlined the issues for consideration, including the general format, definition of terms, whether other antigens or preparations needed to be added, and other issues. Dr. Katz and the Committee made it clear that they needed to do some homework and phone calling to colleagues in the field after this meeting to be able to address certain issues, such as recommendations for vaccinating persons having chronic immunosuppressive therapy, bone marrow transplantation, steroids, and adrenocorticotropic hormone (ACTH). However, several of the points raised by Dr. Grabowsky were finalized.

Before adjourning, Dr. Katz announced that this would be the last meeting for Dr. Georges Peter and Dr. David Fedson to serve as liaison members of the ACIP. The ACIP joined in applause to thank them for their contributions.

Summary of Agreed-Upon Actions

Following is a "reminder" listing of agreed-upon actions. For more details, see the related section of the minutes.

1. CDC will arrange to publish the ACIP DTP Statement soon in the MMWR, after Dr. Steve Cochi and Dr. Mortimer work out minor changes.

2. Dr. Steve Cochi said he would discuss with Dr. Walt Orenstein the feasibility of publishing in the *MMWR* that monovalent pertussis vaccine is now available outside of Michigan; he also agreed to create a section in the DTP Statement on the role of acetaminophen and to list it in the Table of Contents.

3. Dr. Lauri Markowitz agreed to call authors of the *JAMA* article on measles vaccination of children with upper respiratory infections to see if they have any paired sera available that CDC could test for rises to other viruses.

4. Mr. Steve Sepe said he would give the ACIP a copy of a brochure created by the NVP on the Immunization Education and Action Committee, a subcommittee of the Healthy Mothers, Healthy Babies Coalition.

5. Dr. Katz and other Committee members agreed to do some "homework" and phone calling to colleagues in the field to

address certain issues--such as immunization for persons having chronic immunosuppressive therapy, undergoing bone marrow transplantation, or having treatment with steroids and ACTH--addressed in the proposed ACIP statement on immunization of persons with altered immunocompetence.

6. CDC agreed to make several suggested changes in the ACIP draft statements on hepatitis and on immunization of persons with altered immunocompetence.

The ACIP convened in Auditorium A of the Centers for Disease Control (CDC), Atlanta, Georgia, on June 3-4, 1991, at 8:40 a.m. Samuel Katz, M.D., Wilburt C. Davison Professor, Duke University Medical Center, presided as Chairperson.

Welcome and Opening Remarks

Dr. Katz opened the meeting by asking the members of the ACIP Committee and the others in attendance to introduce themselves and give their affiliations. In attendance were 37 representatives of the pharmaceutical industry, media, academia, armed services, and interested groups, as well as members of local and national government agencies.

Dr. Katz said that all members of the Committee had received correspondence from Mr. Jeffrey H. Schwartz, on behalf of Dissatisfied Parents Together, alleging conflict of interest by some members of the Committee. Dr. Katz said that--as he has personally explained to Mr. Schwartz in the past--those people most knowledgeable in the field of immunization have naturally collaborated in some ways with the people who develop or manufacture vaccines in this country in order to conduct clinical trials of safety, immunogenicity, and efficacy.

To make sure that Committee members were "on solid ground" and in part because of that group's charges, Dr. Katz said that he had asked for clarification from the legal authorities at CDC about what the appropriate stance of CDC and the Public Health Service is regarding alleged conflict of interest. Claire Broome, M.D., Executive Secretary of the ACIP Committee, was asked to summarize CDC's legal position.

Dr. Broome reported that the CDC Committee Management Officer, as well as several executive secretaries of these committees, met with the CDC Office of General Counsel and the CDC ethics office to discuss this issue. She said that the advisory committees to CDC perform a different function than those at the FDA or the National Institutes of Health, in that they constitute a forum for public discussion of the issues and in that members may have association with the pharmaceutical industry or state health departments who receive federal funding. She said the general consensus was that it would be inappropriate to exclude such people from committee membership or to ask them to excuse themselves from discussing these issues. Rather it was felt that the appropriate position was to be sure that people were aware of affiliations that could cause potential conflict of interest. She said that the form of such disclosures was still under discussion.

Dr. Katz and Ms. Cheryl Counts said that Financial Interest Statements were sent out recently (except to new members) and must be updated annually.

Dr. Katz then congratulated Dr. Georges Peter, Dr. Stanley Plotkin and colleagues for the new issue of the report of the American Academy of Pediatric's (AAP's) Committee on Infectious Diseases (Red Book), distributed in late April.

Diphtheria-Tetanus-Pertussis (DTP) Issues

*ACIP DTP Statement.* Dr. Katz then asked Dr. Stephen Cochi to discuss the status of the ACIP DTP Statement. He said that since the last ACIP meeting, the DTP Subcommittee (composed of Drs. James D. Cherry, Samuel Katz, Edward A. Mortimer, Jr., and William Schaffner) had reviewed (1) written comments received from Committee members and Mr. Schwartz and (2) proposed revisions to the February draft of the statement. The subcommittee and CDC held a conference call on May 9 to make further revisions, and a revised statement was issued May 15 and mailed to members.

Dr. Cochi then summarized the key changes and received comments regarding them:

1. p. 17: Three sentences added: "This reassessment has determined that the number of cases [in the National Childhood Encephalopathy Study--NCES] was too small and their classification subject to enough uncertainty to preclude drawing valid conclusions about whether a causal relationship may exist between pertussis vaccine and permanent neurologic damage. Preliminary data from a 10-year followup study of some of the children studied in the original NCES study also suggested a relationship between symptoms following DTP vaccination and permanent neurologic disability (38). However, details are not available to evaluate this study adequately."

Comments: Dr. Mortimer and others requested that the last sentence also add "and the same concerns about coincidence and/or precipitation of symptoms of pre-existing illnesses exist." There seemed to be consensus that this phrase needed to be added, but that the wording should be worked out between Dr. Mortimer and Dr. Cochi.

Dr. Carolyn Hardegree, U.S. Food and Drug Administration (FDA), asked that the phrase "This reassessment by multiple groups. . ." and appropriate references be added to the first sentence in the above addition.

2. p. 18, ll. 17-20: wording changed (see draft); on line 22, the word "demonstrated" has been changed from "proven" to reflect that one cannot prove a negative.

3. p. 19, item 2, the risk estimate from the NCES study of 1:140,000 for serious acute neurologic illness was removed

because conclusion No. 2 focuses on *permanent* brain damage.

4. pp. 26-27, to accompany the section on "Contraindications," a table has been added (Table 4, p. 54). Plus, two contraindications were moved to the "Precautions" list: temperature of 40.5 C or higher within 48 hours not due to another identifiable cause, and collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.

Comments: Dr. Hardegree said that some of this statement's precautions fall under FDA's definition of "warnings," and this might be confusing. The Committee decided to put the word "warning" in parentheses after the word "precaution," and to put a reference in Table 4 to "see the text."

5. p. 26, point 2, the definition of "encephalopathy (not due to another identifiable cause)" has been changed to "an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, generalized or focal seizures that persist more than a few hours, with failure to recover within 24 hours."

6. pp. 28-29, discussion of prolonged febrile seizures was changed.

Comments: Dr. Peter proposed that there be a phrase inserted indicating that this is a generic statement "irrespective of whether or not they are temporally associated with pertussis vaccination" or "irrespective of their cause." Dr. Katz agreed to this change. It was also suggested that these sentences be shortened.

Dr. Cochi then asked if there were any other important changes. It was asked whether monovalent pertussis vaccine is now available outside of Michigan. Dr. Cochi said it was. It was suggested that this be published in the *MMWR*. Dr. Cochi said he would discuss the feasibility of this with Dr. Walter Orenstein.

Dr. Hardegree asked that the wording on p. 9 about candidate vaccines be more cautious so it doesn't imply that the Committee is endorsing these as-yet unlicensed products. It was agreed to put something to the effect that, "In published studies, some of these products appear to be less prone to cause common adverse reactions, etc." It was also suggested that references be added here.

On p. 40, under the section on pertussis prophylaxis for case contacts, it was suggested by Dr. Peter to move "trimethoprim-sulfamethoxazole" and its dosages to another sentence and to make clear that this is an alternative antimicrobial for those who

can't tolerate erythromycin.

On p. 15, line 5, "sterile" was added before "abscesses"; in line 9, "usually" was added before "self-limited." On p. 31, the third-to-last line, the phrase "but not OPV" was deleted.

Dr. Cochi then reviewed the "other changes" listed on p. 2 of his summary handout. These were accepted, except that there was discussion about moving the paragraph on acetaminophen. Liaison representative Dr. Fedson also suggested that the new paragraph be made into a section of its own on "the Role of Acetaminophen" and be named in the Table of Contents. Dr. Katz asked Dr. Cochi to work this out.

Discussion then centered around several changes suggested for Table 3, on p. 53. "High-pitched, unusual cry" was deleted from the list of adverse events since it's not directly addressed in the text. By vote, it was also decided to collapse the event subheadings "Mild/Moderate Systemic" and "More Serious Systemic" into one heading entitled "Systemic."

*Response to Dissatisfied Parents Together.* Dr. Katz noted that Committee members had received voluminous materials from this group. He asked if there were any comments or responses that need to be addressed. The following were mentioned:

1. That every effort be made to comply with the request for citations made by this group.

2. On p. 2, point 2 on the handout, Dr. Orenstein asked if everyone was comfortable with what the statement says about febrile seizures. Members said it reflected statements of the Child Neurology Society and the American Neurological Association, that it had taken one year to be written, and that it should stand as written.

It was decided that the Committee should not delay further in publishing the DTP Statement in the *MMWR*. Dr. Katz acknowledged the tremendous amount of work and time expended by Dr. Cochi and the Committee in preparing the statement.

Hepatitis Statement

Next, Harold Margolis, M.D., brought up several issues for discussion or approval in the revised ACIP Hepatitis Statement, draft 5/20/91, previously mailed to Committee members.

*Proposed Immunization Schedule.* The major issue, he said, was the proposed schedule (Table 4 of draft). This was the primary focus of discussion at the last ACIP meeting, and since then, the Committee on Infectious Diseases of the AAP had also met and wrestled with this issue. Dr. Peter summarized unanimous

recommendations of that AAP committee, which were that the schedule: (1) maximize implementation, (2) provide flexibility for the different circumstances of health care in this country, and (3) coincide with "existing immunization schedules in this country." He said one of the considerations in the private sector is dealing with multiple injections--that giving it at the same time as other childhood vaccinations could lead parents to saying, "One shot, maybe two, but not three." The initiation of vaccination at birth was also discussed. The schedule devised does provide a tremendous amount of flexibility, he said. The AAP Committee on Fetus and the Newborn, which met on June 3, will also make recommendations reflected in the official AAP position, Dr. Peter said.

Dr. Katz was troubled by the phrasing "preferred" and "optional" for the two options in the table, and wondered if just two options couldn't be given. Dr. Plotkin agreed. He said when multivalent vaccines exist, a newborn dose might not be the optimal way of delivery. However, right now, all the pharmaceutical companies are trying to figure out how to combine vaccines; if the Committee sends a message that several different combinations are necessary, this will have an impact on the choices that are made.

Dr. Katz asked representatives of the pharmaceutical companies present to give the Committee an idea of how far in the future such combined children's vaccines are. Dr. Plotkin said all of the companies are working on combinations; some combinations will be available in 1 to 5 years. A representative of Merck, Sharpe and Dohme said that company planned to start studies to combine hepatitis B this year and conjugate *Hemophilus influenzae* vaccines; ones combining DTP will follow. The issue of combining vaccines was given further support by a slide, shown by Dr. Katz, projecting that soon 2-month-olds will be getting four vaccinations at once--something that obviously everyone wants to avoid.

Saul Krugman, M.D., New York University Medical Center, said that birth is unquestionably the preferred option for children in high-risk areas such as Hawaii, and that the statement should mention this, but that otherwise it doesn't make any difference which option is chosen. Dr. Peter said that pediatricians really do want to have a preferred schedule. Dr. Katz said he wanted to return to discuss this issue after Committee members had discussed the rest of the ACIP statement.

*Prenatal Screening.* Prenatal screening for hepatitis was mentioned throughout the above discussion. There is tremendous pressure to stop prenatal screening, but numerous persons indicated that both prenatal and postnatal screening are important. Dr. Margolis said that both AAP committees mentioned, plus a key member of the American College of Gynecologists

(ACOG), feel that this proposed immunization schedule should not be used to eliminate universal maternal screening. Dr. Broome and Gregory Istre, M.D., said that prenatal screening is important in surveillance for locating other household contacts to implement preventive measures.

Dr. Katz asked Dr. Margolis how widespread prenatal screening is nationally. Dr. Margolis said four states that account for almost 40% of the expected antigen-positive women in the United States--California, Hawaii, Michigan, and New York--have laws or official rules mandating screening. Several other states are in the process of such legislation. In talking with the ACOG chairman, Dr. Margolis said he understands it's becoming somewhat more acceptable in that group. Every state but two has perinatal prevention programs within its immunization program.

Dr. Margolis said that there are about 22,000 antigen-positive women "in each year's birth cohort"; an estimated 6,000 children would become infected in the perinatal period each year.

*Discussion of Statement and Changes.* Dr. Margolis then went over changes in the draft since it was last seen by Committee members. These included the following:

1. The prevention of delta infection has been added as a benefit of vaccination.

2. On p.7 and p.11 (No. 5) wording has been added encouraging states to determine susceptibility to hepatitis B infection, when feasible, for household contacts and sexual partners of HBsAg-positive women. Committee discussion emphasized that point 5 should be rewritten for clarity and that care should be taken to emphasize "encouraging," not just "when feasible."

3. On p. 12 a strong statement about the need for immunization of high-risk teens has been added. The Committee suggested stronger language throughout "encouraged" rather than "offered to"; actually specifying what the statement means by "having multiple sexual partners" since many teenagers might be termed "high risk" if that means "more than one sexual partner in the past 6 months"; and actually stating that the widespread immunization of all teenagers is optimal and would create the greatest single impact on the prevention of this disease. Dr. Katz suggested that an immunization schedule for teenagers be included. Another person suggested that a table showing the rising incidence of seroprevalence of hepatitis B in adolescents be included. In short, as Dr. Schaffner phrased it, it was decided that adults should not be treated as "second-class citizens" in this document, and that the recommendations for adults (including teenagers)

should be as forthright, clear, and instructive as they are for children. This discussion led to a unanimous vote to recommend universal immunization for adolescents and children, with the qualifier that the emphasis on immunization of teenagers is a relatively short-term event until the impact of universal immunization is felt. Cost-effectiveness (vaccines for adults cost more) and infrastructure needs were brought up; teen immunization would at least double the number of health-care visits for immunization, one Committee member said, overwhelming some immunization clinics. The logistical difficulty of getting three doses into those teens most at risk of disease was emphasized. The Committee agreed that universal immunization of infants was the highest priority and should not be compromised by universal immunization of adolescents. Also, Dr. Broome noted that the frequency of chronic sequelae from persons acquiring disease during adolescence is much lower than in childhood.

4. On pp. 12-13, the sentence on occupational risk has been amended to read: "HBV [hepatitis B virus] infection is an occupational hazard for health-care workers, *and it is an occupational hazard for public safety workers who have blood exposure in the workplace.*" This change was proposed because the vaccination of public safety workers has caused confusion for some states. In some areas, volunteer playground workers at day-care settings are being required to get vaccinations, for example. Other states are unsure if parole officers and prison guards are included in this category. In other states, Occupational Safety and Health Administration guidelines are being very aggressively enforced, with the result that one state is being asked to provide hepatitis B vaccine to the tune of $2-$3 million to groups who have not had a reported case of this disease in 10 years. Occupational risk data are skimpy, and the Council of State and Territorial Epidemiolo-gists and others have asked for some guidance from the ACIP in this area. After discussion, the Committee decided *not* to provide a list of jobs that should require vaccination. The Committee did emphasize the availability of postexposure prophylaxis for job categories with possible, but unlikely exposures to blood.

5. To deal with the issue of postexposure prophylaxis, Table 2 was created. It was suggested that the phrase *known exposure* be substituted for *defined exposure*, which occurred twice in the table.

6. A Committee member suggested: (a) p. 14, paragraph 9, change heading from "Sexually active homosexual men" to "Sexually active homosexual and bisexual men." (b) p. 15, paragraph 1, change term *multiple partners* to *more than one*

*partner.*

7. The Committee decided not to take the suggestion to explicitly state in the document that sexually transmitted disease clinics and health departments should begin hepatitis B vaccination for every patient who has gonorrhea. The reasons given were that strategies for initiating this have to be examined and the ACIP loses its credibility if it doesn't prioritize. (Some states can't buy vaccines for newborns right now, for example; some have stopped contact-tracing for syphilis because of personnel shortages.)

8. There was discussion about changes in the section on p. 10 about "Side Effects and Adverse Reactions." Dr. Katz asked Roland Levandowski, M.D., with FDA's Center for Biologics Evaluations Research (CBER), to discuss these. Dr. Levandowski said that surveillance is not accurate enough to have a good estimate of the occurrence or association of reported adverse events such as Guillain-Barre syndrome (GBS) and cranial neuropathy. Dr. Margolis said that CDC surveillance of GBS, not yet completed, suggests that reports of GBS have decreased in recent years; he suggested that a statement to the effect that "adverse events should be reported" might be added to the document. Dr. Katz suggested mentioning that large numbers of children have been involved in the large-scale infant immunization programs that have used plasma-derived vaccine in Alaska and Taiwan; postvaccination surveillance of these groups has not detected significantly increased frequency of neurologic or other serious adverse events.

9. On p. 11, Committee members requested that a reference be added about giving infants hepatitis B vaccine within 12 hours of birth; Dr. Margolis agreed to do this. It was also discussed that the wording about giving an infant hepatitis immune globulin "within seven days of birth" on the same page needed to be clarified, since it should really be administered as soon as possible, and the efficacy after 48 hours is not known.

*Proposed Immunization Schedule.* Discussion then returned to the proposed immunization schedule (Table 4). Dr. Plotkin suggested adding a sentence at the end of paragraph 1, p. 12, to go along with Table 4, that would send a signal that combined vaccines may soon be available. This suggestion was accepted and the statement will read as follows: "The development of combination vaccines containing hepatitis B antigen will lead to the option of other schedules in the future."

Smallpox, Vaccinia Statement

Dr. William Atkinson discussed draft No. 7 of the Vaccinia

Vaccine Statement. The following general changes had been made in the document since the ACIP last reviewed it: (1) the entire document had been edited; (2) vaccinia vaccine (versus smallpox vaccine) had been referred to throughout the document; (3) all references to persons working with variola (smallpox) virus had been deleted; (4) all specific references to HIV-vaccinia recombinant trials had been deleted; (5) all new material for discussion had been printed in bold type. (See handout, "Notes on revised version [draft 7]" and revised draft.)

Dr. Atkinson then read over all new or substantially modified sections, as outlined on the handout. All were accepted. However, discussion soon turned to the value of the document, and whether it is appropriate for the ACIP to focus the spotlight on such a small problem. Dr. Katz asked for a vote; the Committee recommended that the Statement not be published as written. Another suggestion to issue a formal ACIP recommendation about vaccinia vaccination for individuals in health-care settings described within the document was also not adopted. However, a recommendation to issue recommendations about vaccinia vaccination for laboratory personnel working with high concentrations of vaccinia in laboratories was passed unanimously. Also passed was the decision to include an informational statement--not a formal recommendation--for health-care workers. Dr. Katz asked Dr. Atkinson and Mary Lou Clements, M.D., to revise the document (1) recommending vaccination for laboratory workers, and (2) stating vaccination "may be considered" or "is optional" for other health-care workers who may be exposed to recombinant vaccinia viruses even though the risk of transmission is probably lower with this group. Dr. Atkinson asked the Committee what they recommended that he say to people who call up and ask for 200 doses of vaccine for their entire staff, including all nurses, physicians, janitors, and dieticians. Dr. Katz suggested saying, "In general, we don't think there's a strong indication for use in these people if they wash their hands and follow other recommended procedures." It was also suggested that the description on p. 6 of those who don't need to be vaccinated be expanded.

Update on Cholera Vaccines

Next, Paul Blake, M.D., Chief, Enteric Diseases Branch, DBMD, CID, introduced cholera team members Dr. David Swerdlow, Dr. Robert Tauxe, Dr. Todd Weber, and Dr. Allen Ries. Dr. Swerdlow then gave an overview of cholera in South America and the current recommenda-tions regarding cholera vaccine.

*The Epidemic in South America.* Epidemic cholera had not been reported from South America since 1895. In late January 1991, toxigenic *Vibrio cholera 01*, serotype Inaba, biotype El Tor, was reported simultaneously from several coastal Peruvian cities. It is likely that the epidemic strain was introduced from Asia or

perhaps Africa. The strain is nonhemolytic. As of May 17, 186,000 probable cases (1% of the population) and 1,537 deaths in Peru had been reported to the Pan American Health Organization (PAHO). The epidemic had also spread to several neighboring countries, with confirmed cases reported in Colombia, Chile, Ecuador, and Brazil. The overall case-fatality rate is 0.6% but has increased as remote areas have been affected. Epidemiologic investigations in two cities heavily affected by the epidemic have implicated unboiled drinking water as the main risk factor. Both cities have large water distribution systems, with many breaks and points of contamination and ineffective chlorination. Control efforts now under way include widespread treatment with oral rehydration therapy and intravenous solutions, when necessary, and efforts to provide emergency chlorination.

*Cholera in the United States.* Cholera has been imported into the United States in four documented instances, with 14 total cases since the epidemic began. Three travelers to Peru and Ecuador, who drank unboiled water or ate high-risk foods, became ill. Eleven persons in two separate incidents became ill after eating crab meat that had been brought into the United States in suitcases of returning travelers. There have been no deaths and no secondary transmission. An education campaign has been directed at U.S. travelers to Peru, Colombia, and Ecuador, and commercial fish from the affected countries are being monitored by the FDA. In general, the risk to travelers touring in areas with cholera is low: it's estimated to be 1/500,000.

An endemic focus of cholera exists in the United States; since 1973, sixty-five cases of domestically acquired cholera have been reported, most associated with uncooked seafood. Sustained transmission has not occurred because of adequate sewage treatment and the availability of clean water. In short, for the U.S. population, the risk of cholera from importation of foods, from travelers to epidemic areas, or from the endemic focus in the Gulf of Mexico is low.

*The Cholera Vaccine.* Attempts to develop an effective cholera vaccine have been ongoing for 75 years. Only one vaccine, administered parenterally, is available in the United States. Only one country, Pitcairn, currently requires evidence of cholera vaccination upon entry. In field trials conducted in areas with endemic cholera, vaccines have only been about 50% effective in reducing the incidence of clinical illness for 36 months; the cholera vaccine does not prevent *Vibrio* excretion or carriage and therefore does not prevent transmission of infection.

Recommendations for the use of cholera vaccine, reviewed by the ACIP in 1988, include that it should not be used to manage contacts of persons with imported cases and that it is not likely to benefit most U.S. travelers. Dr. Swerdlow said that CDC does

not think changes in the current recommendations are warranted because of the epidemic of cholera in South America.

Investigational oral vaccines for cholera are divided into three areas: hybrid; killed oral; and live, attenuated oral vaccines. Hybrid vaccines are constructed using noncholera vaccine strains such as salmonella which serve as carriers for expression of cholera antigens. In one trial in human volunteers in Australia, the vaccine did not provide significant protection against infection, although it did reduce the severity of clinical illness. Two killed oral vaccines have been evaluated. A large field trial was begun in Bangladesh in 1985, using killed vaccine. Protective efficacy for all ages for both vaccines was above 50% at 2 years but fell during the third year. Efficacy was much greater for persons >5 years old than for younger children. For three reasons, it is believed that these vaccines would not be effective in South America: (1) they are most efficacious for older children and adults, so protection would be decreased for the immunologically "naive," which would include many in South America since this is the first pandemic in 100 years; (2) the vaccines provide decreased protection for El Tor, Inaba strains, the strain causing the current South American epidemic; and (3) the vaccines provide decreased protection for severe diarrhea for persons with blood group 0, and over 80% of the population of some South American countries have this blood group.

Initial studies of the third type of vaccine--live, attenuated oral vaccines--showed that they caused frequent diarrheal side effects or had low immunogenicity. Currently, two improved vaccine strains are being tested, both made with a classical Inaba strain. In volunteer studies in Maryland, rates of diarrhea illness were 4%-12%; 96%-98% of volunteers developed significant antibody titers. Efficacy ranged from 62% for Inaba strains to 87% for classical strains. Unfortunately, phase-I trials in Indonesia and Thailand have shown variable results; seroconversion rates were better in students than military recruits. Satisfactory seroconversion rates--70%-90%--were achieved in Indonesian children, but higher doses were necessary than in the Maryland volunteers. Finally, another live, attenuated oral vaccine has been developed at Harvard that may have more immunogenicity; however, efficacy trials have not been performed.

*Committee Discussion.* Following Dr. Swerdlow's presentation, Dr. Katz invited suggestions from the Committee. Dr. Plotkin said that Pasteur-Merieux is committed to making its B subunit and whole cell cholera vaccine available for tests, and, with the support of the World Health Organization (WHO) and PAHO, is trying to find a place in Brazil to do an efficacy trial. He asked for any help that CDC's cholera unit could provide in identifying a place where this trial could be done.

A Committee member asked if there were any subgroups of travelers or others (such as immunocompromised patients) for whom CDC did recommend the vaccine; the answer was no, CDC is making no distinction between high-risk and low-risk groups in its recommendations. In response to what CDC does when someone says they really want the vaccine regardless, Dr. Swerdlow said that CDC only explains its recommendations.

Dr. Swerdlow also indicated that there are multiple breaks in water systems in Peru, including those in major cities, with ample opportunity for widespread contamination.

In response to another question, Dr. Swerdlow said that at this point there is no role for tetracycline prophylaxis because of the risk of developing resistant strains.

Awards for ACIP Members

At this point in the meeting, Dr. Walter Dowdle, Deputy Director of the CDC, thanked all the members of the Committee, the liaison members, and consultants for the work they do. Then he singled out two people in particular for thanks, Drs. Cherry and Caroline Hall, who are rotating off the Committee after serving 4 years. They received certificates and CDC medallions. Dr. Katz also announced that Dr. Stanley Broadnax, not present at this meeting, is also rotating off the ACIP. Dr. Katz acknowledged CDC's tremendous role in educating the ACIP members.

Update on Group B Meningococcal Vaccines

Dr. Bradley Perkins, updated the group on group B meningococcal vaccines, particularly a Cuban vaccine that has been extensively used in Cuba and Brazil. The Ministry of Health in Cuba developed the outer membrane protein vaccine in the early 1980s for an epidemic in that country. It showed 83% efficacy (95% Confidence Interval = 42%-95%) in a Cuban clinical trial. When Sao Paulo, Brazil, had an outbreak of serogroup B *Meningococcus* in 1988, the Cuban vaccine was used. A case-control study in Sao Paulo has revealed an estimated vaccine efficacy of 40%-60%. Major adverse reactions were not identified in Sao Paulo, but 70 children developed purpura following vaccination; 5 had documented thrombocytopenia.

Other group B meningococcal vaccines are being studied. For example, researchers at Walter Reed Hospital developed and recently conducted a field investigation of a vaccine in Chile. The serotype of the strain for this vaccine differs from that in the Cuban vaccine. Those researchers found a relatively low vaccine efficacy (51%, with wide confidence intervals) in their controlled trial. Norwegians are just completing a controlled trial in Norway using a vaccine composed only of meningococcal outer membrane proteins; results should be available soon.

Jennings et al. in Canada and Frasch et al. at the FDA are also both working on new vaccines.

In conclusion, Dr. Perkins said that the estimate of the Cuban vaccine efficacy in Brazil is lower than that found in Cuba. The performance in Brazil suggests that this vaccine is not ready for widespread use. He said that there is a need for standardized and reproducible immunologic and bactericidal assays for serogroup B meningococcus. Finally, an independent comparison of immuno-genicity and bactericidal activity elicited by all the serogroup B candidate vaccines would be useful, he said.

Update on Measles in the United States

*Update on Measles Epidemiology.* Dr. William Atkinson said 5,400 cases of measles have been reported from 36 states thus far in 1991. This represents a 42% decline in measles incidence compared to last year. About 15,000-20,000 cases are projected for the entire year. Thirty-nine percent of all cases are in preschoolers. Similarly, most (15 out of 30) outbreaks thus far this year have been among preschoolers. Only 21% of cases were in appropriately vaccinated persons. Fourteen states have reported outbreaks. The largest thus far this year are in New York City (2,000 cases, 9 deaths), Philadelphia (1,100 cases, 8 deaths), and Los Angeles (900 cases). There have been 21 deaths from measles in 1991, for a case-fatality rate of about 3/1000. The June 7 *MMWR* will have more details on this epidemic.

*Measles Outbreak in New York City.* Dr. Susan Davis, IM, CPS, said that from January through April 1991, nearly 2,000 measles cases and 9 measles-associated deaths were reported from New York City--a substantial increase from 1990 and more than has been reported from that locale in the past decade. As of May 31st, 3,083 cases have been reported. Because of suspected under-reporting of cases, CDC undertook an investigation in late April to estimate reporting efficiency at the health-care provider level and to determine the magnitude of the outbreak. Twelve of the City's 83 hospitals were selected for the study; preliminary results suggest that only 55% of cases were reported to the New York City Health Department. Overall, 230 (19.2%) patients with measles found by hospital review were admitted to the hospital. This and other large outbreaks in the United States--affecting mostly black and Hispanic, unvaccinated youth--reflect the failure of the current immunization strategies to achieve high vaccine coverage levels among these children. In response to the epidemic, health department officials implemented several measures, including recommending that children 6-11 months receive a dose of measles vaccine, vaccinating eligible children in emergency rooms, and mounting a multi-media education campaign. Despite this, 150-200 cases continue to be reported each week. Dr. Atkinson was asked if the incubation period was still about 14 days among nosocomial cases. Dr. Atkinson said

that data he collected last year suggest that the range of rash-to-rash interval is from 1 week to 18 days.

*Measles Vaccination of Children with Upper Respiratory Tract Infections (URIs).* Dr. Lauri Markowitz, IM, CPS, gave two brief presentations. The first was based on recently published data on vaccination of children with URI (*JAMA*, April 1991). The study was designed to investigate whether children with acute upper respiratory infections have a decreased response to MMR vaccination. There were two groups in the study: subjects 15 to 18 months of age with colds, and controls, who were children of the same age who had no history of a cold in the past month and had negative physical examinations. Results showed that 79% of the 47 children with colds responded to the measles component of the vaccine, in contrast to 98% seroconversion rates among the 51 controls. This was a statistically significant difference. Nonresponders were revaccinated, but none were retested to see if they responded to revaccination. This would have been important to rule out other reasons for nonresponse to vaccine, other than the URI at the time of initial vaccination.

The investigators hypothesize that interferon produced by the URI interfered with the measles component. There are problems with this hypothesis, Dr. Markowitz said. First, the data would suggest that interferon was specific for measles. Second, there was no determination of the etiology of the URI. This is important since some agents do produce interferon and others do not. Third, no information was provided on the season of vaccination, which also may have suggested a possible viral agent. Finally, interferon was not measured in pre-vaccination specimens.

Two other studies have looked at the response to measles vaccination in well and ill children; both were conducted in developing countries. The first, performed in Haiti and published in 1985, showed that 79% of 181 ill 6- to 12-month-old children seroconverted, compared to 82% of the 148 well controls. The ill children had URIs at the time of vaccination. The second study, published in 1988, was conducted in Rwanda among 8- to 19-month-olds. Again, in this study no difference was found between the well and ill children (80% of the well children compared with 81% of the ill children responded to measles vaccination). This study included children who had malnutrition, diarrhea, and malaria as well as URIs. CDC feels there should be no change in the ACIP recommendations that state that minor febrile illnesses are not a contraindication to measles vaccination.

However, CDC does plan to continue to examine this issue. CDC has a large, ongoing study in Minnesota and Wisconsin, which will have over 2,000 children enrolled. Although the primary purpose of this study is not to look at whether minor illness affects serologic response to measles vaccination, CDC will be able to

look at this issue, in the context of the study. A second CDC study is being planned for Georgia; it will have a design very similar to the one in *JAMA*.

The Committee expressed agreement with Dr. Markowitz' conclusion that the data thus far do not warrant a change in the ACIP recommendations for minor febrile illnesses. A Committee member asked if CDC could test the paired sera to see if there could have been a rise to other respiratory viruses. Dr. Markowitz said she could call Dr. Jim Bass to see if any paired sera are available.

*Measles and Vitamin A.* Next, Dr. Markowitz briefly reviewed data on measles and vitamin A, mainly as background. If the Committee decides it wants more information on this issue, this will be arranged for a future meeting. Several questions have been raised this year, mainly stimulated by an article on a vitamin A trial that appeared in the *New England Journal of Medicine* last year. The questions that CDC has been asked are: (1) should vitamin A be recommended for children with measles in the United States? and (2) should clinical trials of vitamin A for measles be conducted in the United States?

Most of the studies on vitamin A have been conducted in developing countries. These studies have addressed two basic questions: (1) is vitamin A deficiency a risk factor for severe measles? and (2) does vitamin A supplementation during measles reduce morbidity and mortality? Dr. Markowitz did not review the studies designed to answer the first question. The studies designed to answer the second were hospital-based intervention trials; she reviewed these briefly. There have been three published trials of use of vitamin A in acute measles.

The first was published in 1932 in the *British Medical Journal;* it was performed in London. Some 600 children <5 years of age were divided into two groups--those who did and didn't receive vitamin A. Of the 300 children who did, 11 (4%) died compared with 26 (9%) who didn't--a significant difference. The difference was even more striking among the children <24 months old: 7% of those with vitamin A died compared with 16% of those in the placebo group.

A second trial was performed in 1987 in Tanzania. The age-group of the children in that study was not disclosed, but 85% were <5 years of age. Of the 88 children who received vitamin A, 6 died, whereas there were 12 deaths among the 92 children who received a placebo. This is not statistically significant overall; however, among children <24 months of age, where most of the deaths occurred, 2% of those who received vitamin A died versus 17% of those who didn't receive this supplement. About 14% of the children in this study were marasmic, and malnutrition was a major problem in the area. Twenty-five percent of all children

admitted to the hospital were found to be malnourished.

The third, recently published study was conducted in South Africa (where acute malnutrition is not a major problem, but chronic malnutrition is) among children <13 years of age. Two of 92 children who received vitamin A died, compared to 10 of the 97 children who received a placebo. Again, if the analysis is limited to children <24 months of age, the difference is significant. The last study also looked at morbidity, which was reduced in children who received vitamin A. After this study was published, CDC's International Health Program Office in Togo stopped a similar study, on ethical grounds; in that study of approximately 200 children, no difference in mortality was observed in children who did or did not receive vitamin A. (The overall case-fatality rate in Togo was lower than it was in South Africa, however.)

Serum retinol levels were tested in these studies and found to be low in Tanzania and South Africa.

In 1987, WHO and UNICEF made recommendations for the use of vitamin A in children with measles. Currently, vitamin A is recommended for children with measles in areas where vitamin A deficiency is a recognized problem or where the fatality rate from measles is 1% or higher.

These data and the WHO recommendations have raised concern in the United States, particularly in light of the current measles epidemic. Some questions have arisen:

1. Is there any vitamin A deficiency in the United States?

2. Have any measles deaths occurred in malnourished children?

3. Are there any subpopulations in the United States with measles mortality greater than 1%?

4. Do children with measles in the United States have low serum vitamin A levels?

In response to these questions, Dr. Markowitz said that there is no real, clinically important vitamin A deficiency in the United States. However, NHANES-II data suggest possible subclinical vitamin A deficiency among 3- to 5-year-olds. About 4.6% of the population was found to have serum vitamin A levels in the low range (less than 20 µg/dL). Some sub-groups, such as Hispanics in the Southwest, have lower vitamin A levels. In three outbreaks, case-fatality rates greater than 1% have been seen: among the Samoans in California in 1989 (10% case-fatality rate); among the Hmong in 1990, also in California (4.3%); and in Philadelphia this year among a group with religious exemptions to

vaccination. No deaths in the United States have occurred in children thought to be malnourished. Two recently completed studies have looked at serum retinol levels in measles patients. One was conducted in New York City, where 22% of measles patients <2 years of age had serum retinol levels less than 20 µg/dL. In Milwaukee, 71% of children <5 years of age (80% of the children in this study had been hospitalized with measles) had retinol levels less than 20 µg/dL.

Based on these data, CDC presented the following questions to the ACIP:

1. Should ACIP consider making recommendations about the use of vitamin A? Should any be made at this time?

2. Should clinical trials with vitamin A and measles be conducted in the United States?

Dr. Peter said that the AAP is working on a statement that raises many of the same questions. He felt guidelines may be needed, since questions may be raised about vitamin A toxicity, for example. Following a brief discussion, Dr. Katz said he "sensed that the ACIP is not ready to make a statement on vitamin A and measles."

Neonatal Tetanus Studies in Bangladesh

Dr. Gary Hlady said that Global 2000 and the government of Bangladesh are addressing the problem of neonatal tetanus in that country. A survey in Rajshahi Division revealed that 112 of 330 infant deaths were due to neonatal tetanus, a rate of 18.2 deaths from neonatal tetanus per 1,000 live births. A case-control study showed that a history of two doses of tetanus toxoid was not protective.

All of the tetanus toxoid used in Bangladesh has been produced in that country at a single laboratory facility since 1983. Laboratory procedures were certified by WHO at that time; potency is to be confirmed every 3 years. This was done in 1986, but not in 1989 because the lab was busy tripling its production. Samples from three consecutive lots were sent to WHO in July 1990. Results of WHO testing, reported in October, showed no potency in any of the samples. It is not known when the problem started, as no records are kept of vaccine distribution by lot number.

After the WHO report, vaccine was no longer accepted from the production laboratory. Imported vaccine has been used as of January 1991. The lab was inspected by a team from WHO a couple of months ago; egregious deficiencies were found. The steps needed to bring the facility up to standard have been mapped out. The most important recommendation is that a national vaccine control authority be established in Bangladesh.

Extrapolation of the Rajshahi findings suggests that an estimated 9,000 fatal cases of neonatal tetanus occurred throughout Bangladesh in 1989 alone in children born to women who had received two doses of tetanus toxoid vaccine. The question arises whether this kind of problem exists elsewhere. Tetanus toxoid vaccine is currently being produced in about 50 laboratories throughout the world in 34 different countries. About half of those countries are located in the developing world. Certification in all of these countries is the responsibility of the national control authorities.

Following Dr. Hlady's presentation, members described this as "sobering," "distressing," and "catastrophic." Dr. Broome described this tragedy as a "cautionary tale that might have broader implications." Dr. Hardegree said that there are requirements about what a national control laboratory should look like, and those may be undergoing revision. The meeting was then adjourned for the day at 4:45 p.m.

The meeting was called to order on June 3 at 9:05 a.m. Before presentations were heard, the group decided on meeting dates for 1992. These are: February 12-13; June 9-10; and October 21-22.

Update on the National Vaccine Program (NVP)

Mr. Stephen Sepe discussed the activities of the NVP since the release of the Measles "White Paper" (*The Measles Epidemic: the Problems, Barriers and Recommendations*); described the crisis with the National Vaccine Injury Compensation Program; and described collaborative efforts between CDC and the Office of the Surgeon General.

*Follow-up on Measles White Paper.* One of the recommendations in the paper was to enhance grassroots consumer demand and community support for immunization. Many voluntary organizations had been asking CDC what they could do about the current measles epidemic. In April an initial meeting of interested organizations met to establish strategies and goals. Called the Immunization Education and Action Committee, it is a subcommittee of the Healthy Mothers, Healthy Babies Coalition. Its chairperson is Surgeon General Antonia Novello, M.D., M.P.H. Among the 34 participants were representatives from the Association of Junior Leagues International; the National Parent Teachers Association; Children's Action Network; Voluntary Hospitals of America; Robert Wood Johnson Foundation; Catholic Health Association; representatives of the AMA, AAP, and American Nurses Association; the March of Dimes; the National Council of La Raza; Delta Sigma Theta Sorority; National Association of Community Health Centers; the Association of State and Territorial Health Officers; Rotary International; and numerous federal agencies, including CDC. Many of these organizations have already launched immunization campaigns. CDC's Division of Immunization would like to fund

Healthy Mothers, Healthy Babies and serve in a coordinating role, providing information to develop informed advocates and community leaders. The Division of Immunization is putting together a brochure describing the committee and its functions; Dr. Katz asked that the ACIP be provided with it, when it's published. The next meeting of this group was scheduled for June 18.

Another recommendation of the White Paper was to coordinate immunization services of federal agencies. In response, an Interagency Committee on Immunization has been formed and held its first meeting on February 22. Ken Bart, M.D., is the chairperson. Participants of this group include CDC; HRSA; Indian Health Service; Office of the Assistant Secretary for Planning and Evaluation; Office of Health Planning and Evaluation; Office of Minority Health; Office of the Surgeon General; National Institutes of Health; Department of Agriculture; Department of Housing and Urban Development; Department of Education; Health Care Financing Administration; National Vaccine Advisory Committee; National Vaccine Program Office; and the Administration for Children and Families. This committee is already working on a draft of a plan to address the recommendations of the Measles White Paper.

A Subcommittee on Access to Services within the National Vaccine Advisory Committee has been formed to review third-party payment plans, focusing on barriers to access. Its first meeting was held on May 13. Ed Marcuse, M.D., University of Washington School of Medicine, is chairperson. A Subcommittee on Vaccine Licensure and Regulation has been formed to review specific licensing and regulatory processes and to recommend improvements in the licensing/regulatory process. Robert Gerety, M.D., Biogen, Inc., Cambridge, Massachusetts, is chairperson. Its first meeting was held on May 9.

*National Vaccine Injury Compensation Program.* Mr. Sepe then updated the status of this program, which he described as being in crisis. As of May 14, 4,078 retrospective (filed before October 1988) and 188 prospective (filed after October 1988) petitions had been filed. In the history of the U.S. Claims Court, the most petitions the Court had heard in a single year for any one program was 800; there was one week with the vaccine compensation program when 3,000 petitions were filed. (Most petitions concern DTP vaccine; more than 20 lawyers have filed more than 20 cases each--in fact, for 21 or 22 lawyers, there were 800-900 cases filed.)

This is a major stress on the Department of Justice. The crisis is not just in numbers, but in funding. In 181 awards thus far, $108.4 million has been paid to petitioners and for attorney fees in cases for which compensation was denied. At this rate, the funding for 1991 will be expended by June. To handle all the cases before it, $2-3 billion may be needed. A position paper is

being drafted. The Advisory Commission on Childhood Vaccines voted at its last meeting to have a moratorium on payment. Staggered payments and the use of "prospective dollars" have also been suggested options.

*Collaborative Activities with the Office of the Surgeon General.* Finally, Mr. Sepe summarized the activities of the Office of the Surgeon General demonstrating her commitment to immunization. These are:

1. She has named immunization as one of her top priorities.

2. She has held immunization briefings.

3. She is chairperson of the Immunization Education and Action Committee.

4. She is involved in the Healthy Children Ready to Learn Initiative.

5. She helped create the Interagency Committee on Immunization.

6. She has conducted site visits to problem areas.

7. She is considering a Surgeon General's Report on Immunization.

*Committee Discussion.* Subsequent ACIP discussion focused primarily on the crisis in the National Vaccine Injury Compensation Program. Dr. Walt Orenstein pointed out that, to CDC's knowledge, the peak number of lawsuits filed against DTP vaccine manufacturers was 255 in 1986; if the compensation program folds and many of these cases go into the court system, we may be seeing a "potential disaster" in defense costs alone.

Update on Influenza Vaccines

Dr. Robert Chen brought the Committee up-to-date on the investigation of GBS cases possibly associated with the 1990-91 influenza vaccination. He said that the Army recently published data on months of onset of 289 cases of GBS among all Army individuals during a 9-year period (1980-88). An average of about 80% of 780,000 active-duty individuals received influenza vaccine each October. No increases in onset of GBS cases was observed during the ensuing months, suggesting that flu vaccine was not associated with GBS during these years.

Dr. Chen said that since his last report to the Committee in February, no new cases of GBS following 1990-91 flu vaccination have been reported to the passive surveillance system--the

Vaccine Adverse Events Reporting System (VAERS). Previously, Dr. Chen had reported that, based on best estimates of age-specific vaccine coverage, no association had been found between the flu vaccination and GBS in persons ≥65 years of age, but that slightly elevated relative risks, at significant levels, may exist for individuals 18 to 64 years old. However, perhaps a more accurate interpretation of the latter finding would be that the assessment of the risk of GBS for 18- to 64-year-old flu vaccine recipients awaits more accurate denominator data. CDC has contracted for vaccine coverage surveys of the sites included in the numerator. The surveys will include a questionnaire on the receipt and timing of the flu vaccine and the presence of ACIP indications for flu vaccination. Results are expected before the next ACIP meeting. Dr. Chen said that if the risk of GBS following the 1990-91 flu vaccine was similar to swine flu, when the incidence was 1 case of GBS per 100,000 vaccinees, the excess cases should be detectable through the active and passive surveillance systems set up for this year.

Committee and audience comments indicated that the three distinct components of the swine flu GBS outbreak--namely, distinct temporal clustering of cases after vaccination; low antecedent illness rates in vaccine-related cases; and high incidence rates--do not appear to be evident in 1990-91; all indications are that we do not have an outbreak now. As one Committee member phrased it, "Is the juice worth the squeeze?" At what point, he asked, is CDC willing to just stop this investigation, because the number of cases is too small and the expenditure of CDC resources so considerable--especially at a time when all government agencies are feeling the pinch of constrained resources?

S. William Berg, Captain, Medical Corps, U.S. Navy Environmental Health Center, updated the Committee on GBS cases in the Navy. He said that 118,000 recruits had been vaccinated as of the end of May; only 1 case of GBS had occurred, and he had also received MMR, oral poliovirus vaccine, and adenovirus vaccine.

Dr. Chen said that he had spoken to an Army representative, who said no GBS cases had been reported among Desert Shield recruits, in whom some 300,000 vaccinations had been given.

Immunization of Immunocompromised Individuals

Dr. Mark Grabowsky reviewed a draft ACIP Statement on Immunization of Persons with Altered Immunocompetence, dated June 3, 1991, and handed out to Committee members. He pointed out that this document differs from other ACIP statements in form and content in that it is mainly a summarized, user-friendly compilation of existing statements. With very few exceptions, there are no new data or recommendations. Its purpose is to assist those who provide care for immunocompromised patients in making decisions on immunization.

Dr. Grabowsky first defined the terms used in the document: *recommended* ("the vaccine is either recommended as part of the routine schedule or the medical condition represents an indication for use of the vaccine"); *not contraindicated* ("the category of immunosuppression is not a contraindication to the use of the vaccine"); and *contraindicated* ("the medical condition represents either an absolute or relative contraindication to the use of the vaccine.")

The issues for consideration before the Committee, he said, were:

1. General format (a two-page introduction; three tables of recommendations; and an extensive set of footnotes compiled from existing ACIP statements)

2. Whether or not to expand the introductory section on "Altered Immunocompetence."

3. Several areas with potential ambiguity were discussed. No guidance is offered to the clinician as to how disease categories are defined, for example. Within each disease category, the degree of immunocompetence may vary according to the severity of the disease. There is no subclassification by degree of immunosuppression.

4. The statement offers no additional explanation, outside of the footnotes, why each recommendation was made. Does the Committee recommend fuller discussions of the reasons for these recommendations?

5. Some disease categories that may be associated with immunosuppression may need to be added, combined or removed. These include bone marrow transplantation, radiation exposure, heavy metal exposure, and alcoholic cirrhosis.

6. What other antigens or preparations may need to be included (such as HBIG, VZIG, and vaccinia vaccine)?

7. Specific guidance is needed from the ACIP regarding DTP (Td) recommendations for those on chronic immunosuppressive therapy for allografts (Table 1).

Dr. Katz and others first made it clear that Committee members needed to do some "homework" and phone calling to colleagues in the field to address certain issues, subsequently identified as: DTP (Td) for persons with allografts on chronic immunosuppressive therapy, and immunization of patients undergoing bone marrow transplantation or receiving treatment with steroids and adrenocorticotropic hormone (ACTH). However, the following issues were resolved:

1. The term *not contraindicated* was changed to *Use, if Indicated.*

2. In Table 1, it is acceptable to state that MMR is "recommended/considered" for HIV-infected individuals.

3. In Table 1, HBV was moved to "Routine Infant Immunizations."

4. A footnote on BCG vaccine needs to be added.

5. A line for various immune globulins, including rabies and vaccinia, needs to be added as a footnote.

6. Regarding the shaded areas on Table 2: influenza for alcoholic cirrhosis was left as "recommended"; HBV for HIV-infected persons was changed to "use, if indicated."

7. Another column on "Bone Marrow Transplantation" and a footnoted statement on the complexities of this issue were recommended to be added to Table 2. However, more homework is needed before this can be done.

8. The columns "Chronic Immunosuppressive Therapy" and "Malignancies" on Table 2 should be collapsed into one column.

9. It was agreed to differentiate between those on cancer chemotherapy and those not.

10. A boldface footnote clearly stating that children who are taking steroids for asthma are not considered immunosuppressed needs to be added.

Before adjourning, Dr. Katz announced that this would be the last meeting for Dr. Peter and Dr. Fedson to serve as liaison members of the ACIP. The ACIP joined in applause to thank them for their contributions.

Dr. Katz adjourned the meeting at 11:35 p.m.

I hereby certify that, to the best of my knowledge, the foregoing summary of minutes is accurate and complete.

Samuel L. Katz

Samuel L. Katz, MD, Chairperson
Date: 4 September 1991

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